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(54) Title: METHODS FOR TREATING AND PREVENTING MIGRAINES

(57) Abstract: The invention provides safe and effective methods for treating and preventing migraines by administering an effective amount of one or more cholinesterase inhibitors and, optionally, one or more migraine drugs. The invention also provides composition, combinations and kits comprising one or more cholinesterase inhibitors and one or more migraine drugs. In one embodiment, the cholinesterase inhibitor is donepezil or ARICEPT®.

Methods for Treating and Preventing Migraines

Related Applications

This application claims priority to US Provisional Application No. 60/349,244 filed January 18, 2002, and US Provisional Application No. 60/323,310 filed September 20, 2001, the disclosures of which are incorporated by reference herein in their entirety.

Field of the Invention

The invention provides methods for treating and preventing migraines by administering an effective amount of one or more cholinesterase inhibitors and, optionally, one or more migraine drugs. The invention also provides compositions and kits comprising an effective amount one or more cholinesterase inhibitors and an effective amount of one or more migraine drugs. A preferred cholinesterase inhibitor is donepezil or ARICEPT®.

Background of the Invention

Migraines are benign recurring headaches and/or neurologic dysfunctions. Classic migraine (sometimes referred to as a migraine with an aura) refers to the syndrome of a severe, throbbing headache which is often preceded by sensory, motor, and/or visual symptoms, referred to as an "aura." Common migraines are sometimes referred to as a migraine without an aura. Common migraines are the most frequent headache type reported by patients.

The migraine aura is thought to be caused by a cortical spreading depression (a slowly spreading depolarization of neurones and glial cells), and the pain may be due to depolarization of perivascular nerve terminals cortically and/or around the large basal cerebral and extracerebral arteries. This, however, does not explain the pain in migraine without aura. On the basis of animal experiments, it has been suggested that migraine pain is due to perivascular neurogenic inflammation around dural and meningeal arteries. This process is known to be associated with liberation of neuropeptide transmitters from perivascular trigeminal nerve endings.

Many drugs are available for preventing and treating migraines, such as propranolol, amitriptyline, valproate, verapamil, phenelzine, and methysergide. Aspirin-like drugs, including aspirin, naproxen, ibuprofen, mefenamic acid, flufenamic

acid, and tolfenamic acid are also used as prophylactic agents. The high dosage of these compounds required for effectiveness is a drawback. It has been estimated that the probability of success with any one of the available prophylactic antimigraine drugs is about 60 to 75%.

There is a need in the art for new treatments for migraines. The invention is directed to this, as well as other, important ends.

Summary of the Invention

The invention provides methods for treating and preventing migraines in a patient in need thereof by administering an effective amount of at least one cholinesterase inhibitor. The migraines can be classic migraines, common migraines, complicated migraines, and/or cluster headaches. In other embodiments, the migraines can be menstrual migraines, premenstrual migraines, ophthalmic migraines, and/or ophthalmoplegic migraines. In other embodiments, the migraines can be fulgurating migraines, Harris' migraines, and/or hemiplegic migraines. In still other embodiments, the migraines can be abdominal migraines. The cholinesterase inhibitor is preferably donepezil, a stereoisomer thereof, and/or a pharmaceutically acceptable salt thereof.

The invention provides methods for treating and preventing migraines in a patient in need thereof by administering an effective amount of at least one cholinesterase inhibitor and at least one migraine drug. The cholinesterase inhibitors and migraine drugs can be administered separately or in the form of a composition. The migraines can be classic migraines, common migraines, complicated migraines, and/or cluster headaches. In other embodiments, the migraines can be menstrual migraines, premenstrual migraines, ophthalmic migraines, and/or ophthalmoplegic migraines. In other embodiments, the migraines can be fulgurating migraines, Harris' migraines, and/or hemiplegic migraines. In still other embodiments, the migraines can be abdominal migraines. The cholinesterase inhibitor is preferably donepezil, a stereoisomer thereof, and/or a pharmaceutically acceptable salt thereof.

The invention provides compositions and combinations comprising one or more cholinesterase inhibitors and one or more migraine drugs. The invention provides kits comprising one or more cholinesterase inhibitors and one or more migraine drugs, where the cholinesterase inhibitors and migraine drugs are separate components in the kit or are in the form of a composition in the kit.

Detailed Description of the Invention

"Patient" refers to animals, preferably mammals, more preferably humans. The term "patient" includes adults and children, and men and women. Children includes neonates, infants, and adolescents.

"Migraine" refers to periodic, hemicranial, throbbing headaches that can be accompanied by nausea and/or vomiting. Migraines can occur in children and adults, and men and women. "Migraine" includes classic migraines, common migraines, complicated migraines, cluster headaches, menstrual migraines, premenstrual migraines, ophthalmic migraines, ophthalmoplegic migraines, fulgurating migraines, Harris' migraines, and/or hemiplegic migraines. Neurologic symptoms can occur which are caused by migraines, bur which are not followed by a headache. For example, abdominal pain and vomiting can occur without headache as the sole expression of a migraine. *See* Harrison's Principles of Internal Medicine, 12th Edition, McGraw-Hill, Inc. Chapter 18 (1991).

"Classic migraines" generally begin with neurologic symptoms such as visual scintillations, dazzling zigzag lines, photophobia and spreading scotomas, or dizziness and tinnitus. Classic migraines can have premonitory symptoms such as feelings of elation, excessive energy, thirst, cravings for sweets, and/or drowsiness. At other times, classic migraines can have premonitory symptoms such as a slowing of mentation, a feeling of impending doom, and/or depression. At other times, there can be no premonitory symptoms. *See* Harrison's Principles of Internal Medicine, 12th Edition, McGraw-Hill, Inc. Chapter 18 (1991).

"Common migraines" generally have an unheralded onset of headache that can be accompanied by nausea and/or vomiting. Unlike the classic migraine, the common migraine generally does not have neurologic symptoms that occur prior to the onset of the headache. *See* Harrison's Principles of Internal Medicine, 12th Edition, McGraw-Hill, Inc. Chapter 18 (1991).

"Complicated migraines" refers to migraines accompanied by neurologic symptoms (e.g., such as those described for classic migraines) that can either precede or accompany the headache. In complicated migraines, numbness and tingling of the lips, face, hand, arm, and/or leg on side of the body can occur, sometimes in combination with aphasic disorder. The arm and/or leg can become weak or paralyzed on one side,

mimicking a stroke. The numbness or weakness can spread from one part of the body to another slowly over a period of minutes. "Complicated migraines" include basilar migraines. In basilar migraines, the visual disorder and paresthesias are bilateral and can be accompanied by confusion, stupor, coma, aggressive outbursts, vertigo, diplopia, and/or dysarthria. Basilar migraines occur in 30% of children with migraines. *See* Harrison's Principles of Internal Medicine, 12th Edition, McGraw-Hill, Inc. Chapter 18 (1991).

"Cluster headaches" are also called paroxysmal nocturnal cephalalgia, migrainous neuralgia, histamine headache, and Horton's syndrome. Cluster headaches are characterized by constant, unilateral orbital pain, with onset usually within two or three hours after falling asleep. The pain can be intense and steady with lacrimation, blocked nostril, then rhinorrhea, and sometimes miosis, ptosis, flush, and edema of cheek. *See* Harrison's Principles of Internal Medicine, 12th Edition, McGraw-Hill, Inc. Chapter 18 (1991).

"Menstrual migraines" refer to migraine headaches that can generally occur from about 2 days prior to a woman's menstrual cycle until about 3 days after a woman's menstrual cycle. In another embodiment, menstrual migraines refer to migraine headaches that can generally occur from about 2 days prior to a woman's menstrual cycle and that generally end on the last day of the woman's menstrual cycle. Menstrual migraines can occur or re-occur at any time during the menstrual cycle.

"Premenstrual migraines" are migraine headaches that can generally occur from about 7 days prior to a woman's menstrual cycle to about 3 days prior to a woman's menstrual cycle. Premenstrual migraines can occur or re-occur at any time during the premenstrual cycle.

"Ophthalmic migraines" are migraine headaches that are generally accompanied by a marked disturbance of vision.

"Ophthalmoplegic migraines" are migraine headaches associated with paralysis of the eye muscles.

"Fulgurating migraines" are migraine headaches characterized by an abrupt beginning and severity.

"Harris' migraine" is also known as periodic migrainous *neuralgia.*

"Hemiplegic migraines" are a form of migraine headache associated with

transient hemiplegia.

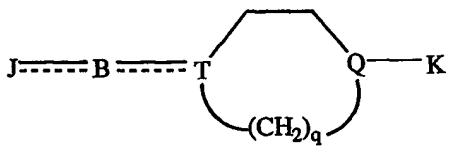
"Abdominal migraines" are characterized by paroxysmal abdominal pain without apparent cause.

"Treating" refers to eliminating the migraine or alleviating one or more symptoms of the migraine (e.g., compared to the symptoms prior to administering one or more cholinesterase inhibitors and, optionally, one or more migraine drugs). Treating encompasses alleviating the number of migraines, the intensity of the migraines and/or the duration of the migraines.

The invention provides methods for treating and preventing migraines (including classic migraines, common migraines, complicated migraines, cluster headaches, menstrual migraines, premenstrual migraines, ophthalmic migraines, ophthalmoplegic migraines, fulgurating migraines, Harris' migraines, hemiplegic migraines, abdominal migraines) by administering to a patient in need thereof a therapeutically effective amount of at least one cholinesterase inhibitor.

The cholinesterase inhibitor can be any known in the art. Exemplary cholinesterase inhibitors include donepezil, tacrine, physostigmine, rivastigmine, galantamine, citicoline, velnacrine maleate, metrifonate, heptastigmine, and the like.

The cholinesterase inhibitor can be a compound of formula I, a stereoisomer thereof, and/or a pharmaceutically acceptable salt thereof:



I

wherein J is

(a) a substituted or unsubstituted group selected from the group consisting of (1) phenyl, (2) pyridyl, (3) pyrazyl, (4) quinolyl, (5) cyclohexyl, (6) quinoxalyl, and (7) furyl;

(b) a monovalent or divalent group, in which the phenyl can have one or more substituents selected from (1) indanyl, (2) indanonyl, (3) indenyl, (4) indenonyl, (5) indanedionyl, (6) tetralonyl, (7) benzosuberonyl, (8) indanolyl, and (9) C_6H_5-CO-CH(CH_3)-;

(c) a monovalent group derived from a cyclic amide compound;

(d) a lower alkyl group; or

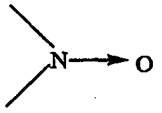
(e) a group of R^{21}-CH=CH-, in which R^{21} is hydrogen or a lower alkoxycarbonyl group;

B is -$(CHR^{22})_r$-, -CO-$(CHR^{22})_r$-, -NR^4-$(CHR^{22})_r$-, -CO-NR^5-$(CHR^{22})_r$-, -CH=CH-$(CHR^{22})_r$-, -OCOO-$(CHR^{22})_r$-, -OOC-NH-$(CHR^{22})_r$-, -NH-CO-$(CHR^{22})_r$-, -CH_2-CO-NH-$(CHR^{22})_r$-, -$(CH_2)_2$-NH-$(CHR^{22})_r$-, -CH(OH)-$(CHR^{22})_r$-, =$(CH-CH=CH)_b$-, =CH-$(CH_2)_c$-, =$(CH-CH)_d$=, -CO-CH=CH-CH_2-, -CO-CH_2-CH(OH)-CH_2-, -$CH(CH_3)$-CO-NH-CH_2-, -CH=CH=CO-NH-$(CH_2)_2$-, -NH-, -O-, -S-, a dialkylaminoalkyl-carbonyl or a lower alkoxycarbony;

wherein R^4 is hydrogen, lower alkyl, acyl, lower alkylsulfonyl, phenyl, substituted phenyl, benzyl, or substituted benyl; R^5 is hydrogen, lower alkyl or phenyl; r is zero or an integer of about 1 to about 10; R^{22} is hydrogen or methyl so that one alkylene group can have no methyl branch or one or more methyl branches; b is an integer of about 1 to about 3; c is zero or an integer of about 1 to about 9; d is zero or an integer of about 1 to about 5;

T is nitrogen or carbon;

Q is nitrogen, carbon or



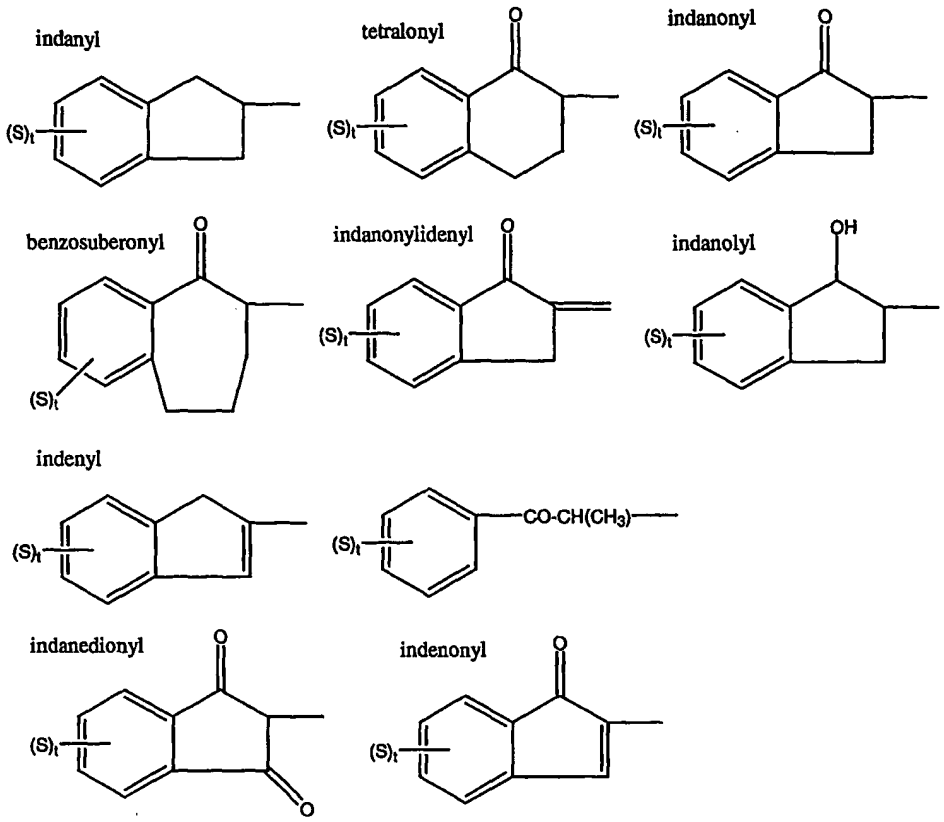
;

q is an integer of about 1 to about 3;

K is hydrogen, phenyl, substituted phenyl, arylalkyl in which the phenyl can have a substituent, cinnamyl, a lower alkyl, pyridylmethyl, cycloalkylalkyl, adamantanemethyl, furylmenthyl, cycloalkyl, lower alkoxycarbonyl or an acyl; and

⁼⁼⁼⁼⁼ is a single bond or a double bond.

In the compound of formula I, J is preferably (a) or (b), more preferably (b). In the definition of (b), a monovalent group (2), (3) and (5) and a divalent group (2) are preferred. The group (b) preferably includes, for example, the groups having the formulae shown below:



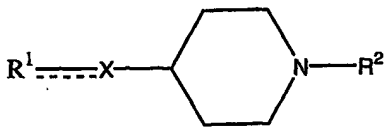
wherein t is an integer of about 1 to about 4; and each S is independently hydrogen or a substituent, such as a lower alkyl having 1 to 6 carbon atoms or a lower alkoxy having 1 to 6 carbon atoms. Among the substituents, methoxy is most preferred. The phenyl is most preferred to have 1 to 3 methoxy groups thereon. $(S)_t$ can form methylene dioxy groups or ethylene dioxy groups on two adjacent carbon atoms of the phenyl group. Of the above groups, indanonyl, indanedionyl and indenyl, optionally having substituents on the phenyl, are the most preferred.

In the definition of B, $-(CHR^{22})_r-$, $-CO-(CHR^{22})_r-$, $=(CH-CH=CH)_b-$, $=CH-(CH_2)_c-$ and $=(CH-CH)_d=$ are preferable. The group of $-(CHR^{22})_r-$ in which R^{22} is hydrogen and r is an integer of 1 to 3, and the group of $=CH-(CH_2)_c-$ are most preferable. The preferable groups of B can be connected with (b) of J, in particular (b)(2).

The ring containing T and Q in formula I can be 5-, 6- or 7-membered. It is preferred that Q is nitrogen, T is carbon or nitrogen, and q is 2; or that Q is nitrogen, T is carbon, and q is 1 or 3; or that Q is carbon, T is nitrogen and q is 2.

It is preferable that K is a phenyl, arylalkyl, cinnamyl, phenylalkyl or a phenylalkyl having a substituent(s) on the phenyl.

In preferred embodiments, the cyclic amine compounds of formula I are the piperidine compounds of formula II, a stereoisomer thereof, and/or a pharmaceutically acceptable salt thereof:



II

wherein R^1 is a (1) substituted or unsubstituted phenyl group; (2) a substituted or unsubstituted pyridyl group; (3) a substituted or unsubstituted pyrazyl group; (4) a substituted or unsubstituted quinolyl group; (5) a substituted or unsubstituted indanyl group; (6) a substituted or unsubstituted cyclohexyl group; (7) a substituted or unsubstituted quinoxalyl group; (8) a substituted or unsubstituted furyl group; (9) a monovalent or divalent group derived from an indanone having a substituted or unsubstituted phenyl ring; (10) a monovalent group derived from a cyclic amide compound; (11) a lower alkyl group; or (12) a group of the formula R^3-CH=C-, where R^3 is a hydrogen atom or a lower alkoxycarbonyl group;

X is $-(CH_2)_n-$, $-C(O)-(CH_2)_n-$, $-N(R^4)-(CH_2)_n-$, $-C(O)-N(R^5)-(CH_2)_n-$, $-CH=CH-(CH_2)_n-$, $-O-C(O)-O-(CH_2)_n-$, $-O-C(O)-NH-(CH_2)_n-$, -CH=CH-CH=CO-, $-NH-C(O)-(CH_2)_n-$, $-CH_2-C(O)-NH-(CH_2)_n-$, $-(CH_2)_2-C(O)-NH-(CH_2)_n-$, $-CH(OH)-(CH_2)_n-$, $-C(O)-CH=CH-CH_2-$, $-C(O)-CH_2-CH(OH)-CH_2-$, $-CH(CH_3)-C(O)-NH-CH_2-$, $-CH=CH-C(O)-NH-(CH_2)_2-$, a dialkylaminoalkylcarbonyl group, a lower alkoxycarbonyl group;

where n is an integer of 0 to 6; R^4 is a hydrogen atom, a lower alkyl group, an acyl group, a lower alkylsulfonyl group, a substituted or unsubstituted phenyl group, or a substituted or unsubstituted benzyl group; and R^5 is a hydrogen atom a lower alkyl group or a phenyl group;

R^2 is a substituted or unsubstituted phenyl group; a substituted or unsubstituted arylalkyl group; a cinnamyl group; a lower alkyl group; a pyridylmethyl group; a cycloalkylalkyl group; an adamantanemethyl group; or a furoylmethyl group; and

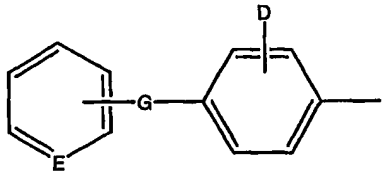
⚊⚊⚊ is a single bond or a double bond.

The term "lower alkyl group" as used herein means a straight or branched alkyl group having 1 to 6 carbon atoms. Exemplary "lower alkyl groups" include methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, pentyl (amyl), isopentyl, neopentyl, tert-pentyl, 1-methylbutyl, 2-methylbutyl, 1,2-dimethylpropyl, hexyl, isohexyl, 1-methylpentyl, 2-methyl-pentyl, 3-methylpentyl, 1,1-dimethylbutyl, 1,2-dimethylbutyl, 2,2-dimethylbutyl, 1,3-dimthyl-butyl, 2,3-dimethylbutyl, 3,3-dimethylbutyl, 1-ethylbutyl, 2-ethylbutyl, 1,1,2-trimethylpropyl, 1,2,2-trimethylpropyl, 1-ethyl-1-methylpropyl, 1-ethyl-2-methylpropyl, and the like. The lower alkyl group is preferably methyl, ethyl, propyl or isopropyl; more preferably methyl.

Specific examples of the substituents for the substituted or unsubstituted phenyl, pyridyl, pyrazyl, quinolyl, indanyl, cyclohexyl, quinoxalyl and furyl groups in the definition of R^1 include lower alkyl groups having 1 to 6 carbon atoms, such as methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, and tert-butyl groups; lower alkoxy groups corresponding to the above-described lower alkyl groups, such as methoxy and ethoxy groups; a nitro group; halogen atoms, such as chlorine, fluorine and bromine; a carboxyl group; lower alkoxycarbonyl groups corresponding to the above-described lower alkoxy groups, such as methoxycarbonyl, ethoxycarbonyl, isopropoxycarbonyl, n-propoxycarbonyl, and n-butyloxycarbonyl groups; an amino group; a lower monoalkylamino group; a lower dialkylamino group; a carbamoyl group; acylamino groups derived from aliphatic saturated monocarboxylic acids having 1 to 6 carbon atoms, such as acetylamino, propionylamino, butyrylamino, isobutyrylamino, valerylamino, and pivaloylamino groups; cycloalkyloxycarbonyl groups, such as a cyclohexyloxycarbonyl group; lower alkylaminocarbonyl groups, such as methylaminocarbonyl and ethylaminocarbonyl groups; lower alkylcarbonyloxy groups corresponding to the above-defined lower alkyl groups, such as methylcarbonyloxy, ethylcarbonyloxy, and n-propylcarbonyloxy groups; halogenated lower alkyl groups, such as a trifluoromethyl group; a hydroxyl group; a formyl group; and lower alkoxy lower alkyl groups, such as ethoxymethyl, methoxymethyl and methoxyethyl groups. The "lower alkyl groups" and "lower alkoxyl groups" in the above description of the substituent include all the groups derived from the above-mentioned groups. The substituent can be one to three of them, which can be the same or different.

When the substituent is a phenyl group, the following group is within the scope

of the substituted phenyl group:



wherein G is -C(O)-, -O-C(O)-, -O-, $-CH_2$-NH-C(O)-, $-CH_2$-O-, $-CH_2-SO_2$-, -CH(OH)-, or $-CH_2-S(\rightarrow O)$-; E is a carbon or nitrogen atom; and D is a substituent.

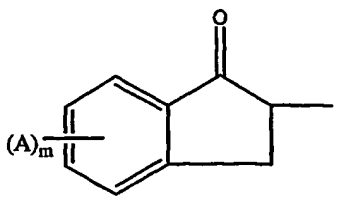
Preferred examples of the substituents (i.e., "D") for the phenyl group include lower alkyl, lower alkoxy, nitro, halogenated lower alkyl, lower alkoxycarbonyl, formyl, hydroxyl, and lower alkoxy lower alkyl groups, halogen atoms, and benzyol and benzylsulfonyl groups. The substituent can be two or more of them, which can be the same or different.

Preferred examples of the substituent for the pyridyl group include lower alkyl and amino groups and halogen atoms.

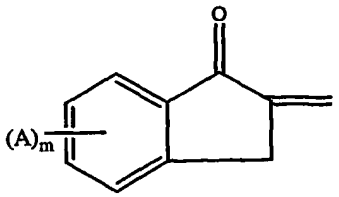
Preferred examples of the substituent for the pyrazyl group include lower alkoxycarbonyl, carboxyl, acylamino, carbamoyl, and cycloalkyloxycarbonyl groups.

With respect to R^1, the pyridyl group is preferably a 2-pyridyl, 3-pyridyl, or 4-pyridyl group; the pyrazyl group is preferably a 2-pyrazinyl group; the quinolyl group is preferably a 2-quinolyl or 3-quinolyl group; the quinoxalinyl group is preferably a 2-quinoxalinyl or 3-quinoxalinyl group; and the furyl group is preferably a 2-furyl group.

Specific examples of preferred monovalent or divalent groups derived from an indanone having an unsubstituted or substituted phenyl ring include those represented by formulas (A) and (B):



(A)



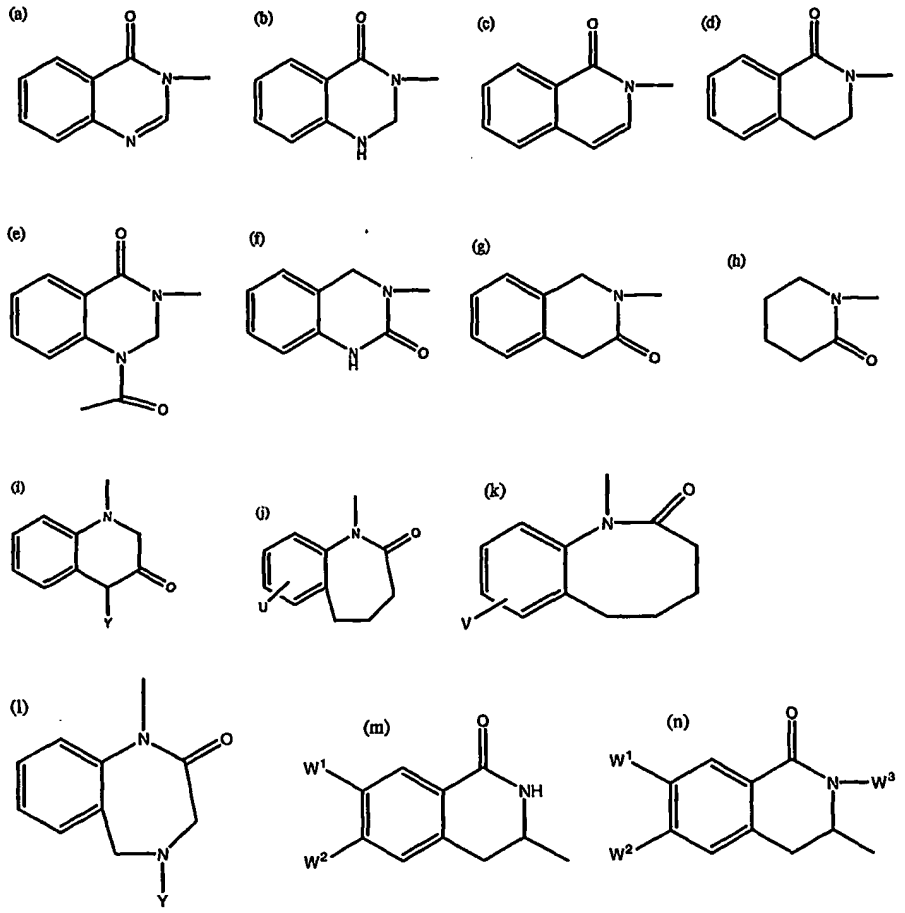
(B)

where m is an integer of from 1 to 4, and each A is independently a hydrogen atom, a lower alkyl group, a lower alkoxy group, a nitro group, a halogen atom, a carboxyl group, a lower alkoxycarbonyl group, an amino group, a lower monoalkylamino group, a lower dialkylamino group, a carbamoyl group, an acylamino

group derived from aliphatic saturated monocarboxylic acids having 1 to 6 carbon atoms, a cycloalkyloxycarbonyl group, a lower alkylaminocarbonyl group, a lower alkylcarbonyloxy group, a halogenated lower alkyl group, a hydroxyl group, a formyl group, or a lower alkoxy lower alkyl group; preferably a hydrogen atom, a lower alkyl group or a lower alkoxy group; most preferably the indanone group is unsubstituted or substituted with 1 to 3 methoxy groups.

Examples of the monovalent group derived from a cyclic amide compound include quinazolone, tetrahydroisoquinolinone, tetrahydrobenzodiazepinone, and hexahydrobenzazocinone. However, the monovalent group can be any one having a cyclic amide group in the structural formula thereof, and is not limited to the above-described specific examples. The cyclic amide group can be one derived from a monocyclic or condensed heterocyclic ring. The condensed heterocyclic ring is preferably one formed by condensation with a phenyl ring. In this case, the phenyl ring can be substituted with a lower alkyl group having 1 to 6 carbon atoms, preferably a methyl group, or a lower alkoxy group having 1 to 6 carbon atoms, preferably a methoxy group.

Preferred examples of the monovalent group include the following:



In the above formulae, Y is a hydrogen atom or a lower alkyl group; V and U are each a hydrogen atom or a lower alkoxy group (preferably dimethoxy); W^1 and W^2 are each a hydrogen atom, a lower alkyl group, or a lower alkoxy group; and W^3 is a hydrogen atom or a lower alkyl group. The right hand ring in formulae (j) and (l) is a 7-membered ring, while the right hand ring in formula (k) is an 8-membered ring.

The most preferred examples of the above-defined R^1 include a monovalent group derived from an indanone having an unsubstituted or substituted phenyl group and a monovalent group derived from a cyclic amide compound.

The most preferred examples of the above-defined X include $-(CH_2)_n-$, an amide group, or groups represented by the above formulae where n is 2. Thus, it is most preferred that any portion of a group represented by the formula R^1------ X—— have a carbonyl or amide group.

The substituents involved in the expressions "a substituted or unsubstituted

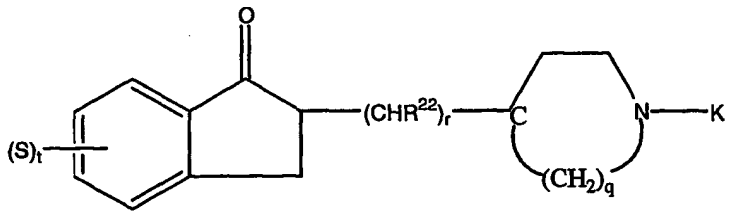
phenyl group" and "a substituted or unsubstituted arylalkyl group" in the above definition of R^2 are the same substituents as those described for the above definitions of a phenyl group, a pyridyl group, a pyrazyl group, a quinolyl group, an indanyl group, a cyclohexyl group, a quinoxalyl group or a furyl group in the definition of R^1.

The term "arylalkyl group" is intended to mean an unsubstituted benzyl or phenethyl group or the like.

Specific examples of the pyridylmethyl group include 2-pyridylmethyl, 3-pyridylmethyl, and 4-pyridylmethyl groups.

Preferred examples of R^2 include benzyl and phenethyl groups. The symbol ⋯⋯ means a double or single bond. The bond is a double bond only when R^1 is the divalent group (B) derived from an indanone having an unsubstituted or substituted phenyl ring, while it is a single bond in other cases.

In preferred embodiments, the compound of formula II is a compound of formula III, a stereoisomer thereof, and/or a pharmaceutically acceptable salt thereof:



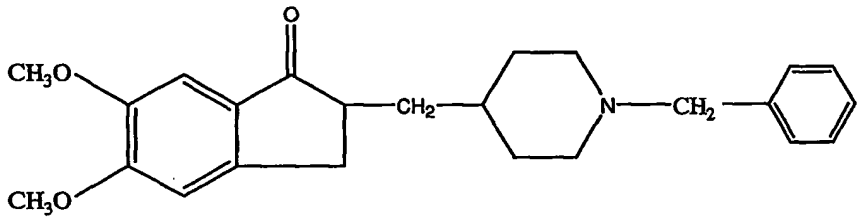
III

wherein r is an integer of about 1 to about 10; each R^{22} is independently hydrogen or methyl; K is a phenalkyl or a phenalkyl having a substituent on the phenyl ring; each S is independently a hydrogen, a lower alkyl group having 1 to 6 carbon atoms or a lower alkoxy group having 1 to 6 carbon atoms; t is an integer of 1 to 4; q is an integer of about 1 to about 3; with the proviso that $(S)_t$ can be a methylenedioxy group or an ethylenedioxy group joined to two adjacent carbon atoms of the phenyl ring.

In preferred embodiments, the compound of formula III is 1-benzyl-4-((5,6-dimethoxy-1-indanon)-2-yl)methylpiperidine; 1-benzyl-4-((5,6-dimethoxy-1-indanon)-2-ylidenyl)methylpiperidine; 1-benzyl-4-((5-methoxy-1-indanon)-2-yl)methylpiperidine; 1-benzyl-4-((5,6-diethoxy-1-indanon)-2-yl)methylpiperidine; 1-benzyl-4-((5,6-methnylenedioxy-1-indanon)-2-yl)methylpiperidine; 1-(m-nitrobenzyl)-

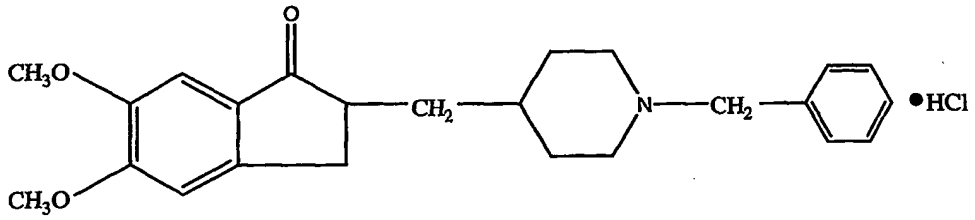
4-((5,6-dimethoxy-1-indanon)-2-yl)methylpiperidine; 1-cyclohexylmethyl-4-((5,6-dimethoxy-1-indanon)-2-yl)methylpiperidine; 1-(m-fluorobenzyl)-4-((5,6-dimethoxy-1-indanon)-2-yl)methylpiperidine; 1-benzyl-4-((5,6-dimethoxy-1-indanon)-2-yl)propylpiperidine; 1-benzyl-4-((5-isopropoxy-6-methoxy-1-indanon)-2-yl)methylpiperidine; 1-benzyl-4-((5,6-dimethoxy-1-oxoindanon)-2-yl)propenylpiperidine; or a stereoisomer and/or pharmaceutically acceptable salt thereof.

In more preferred embodiments, the compound of formula III is 1-benzyl-4-((5,6-dimethoxy-1-indanon)-2-yl)methylpiperidine, a stereoisomer thereof and/or a pharmaceutically acceptable salt thereof, which is represented by formula IV:



IV.

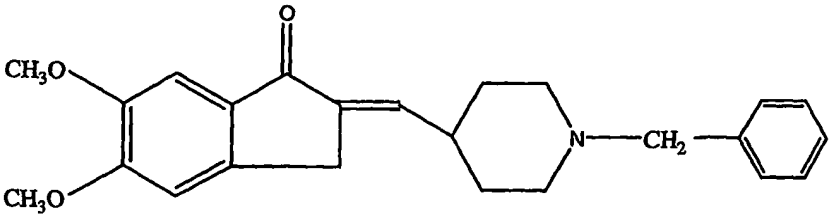
In the most preferred embodiment, the compound of formula III is 1-benzyl-4-((5,6-dimethoxy-1-indanon)-2-yl)methylpiperidine hydrochloride or a stereoisomer thereof, which is also known as donepezil hydrochloride or ARICEPT® (Eisai Inc., Teaneck, NJ), and which is represented by formula IVa:



IVa.

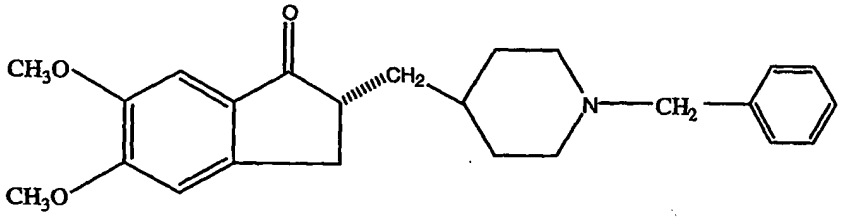
The compounds of the invention can have an asymmetric carbon atom(s), depending upon the substituents, and can have stereoisomers, which are within the scope of the invention. For example, donepezil or pharmaceutically acceptable salts thereof can be in the forms described in Japanese Patent Application Nos. 4-187674 and 4-21670, the disclosures of which are incorporated by reference herein in their entirety.

Japanese Patent Application No. 4-187674 describes a compound of formula V:



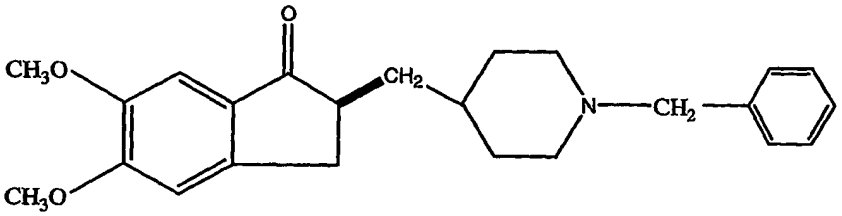
V

which can be in the form of a pharmaceutically acceptable salt, such as a hydrochloride salt. Japanese Patent Application No. 4-21670 describes compounds of formula VI:



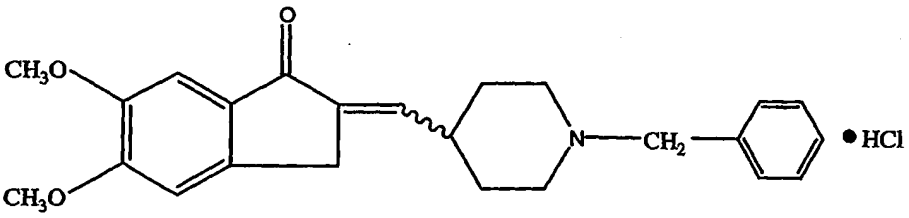
VI

which can be in the form of a pharmaceutically acceptable salt, such as a hydrochloride salt; and compounds of formula VII:



VII

which can be in the form of a pharmaceutically acceptable salt, such as a hydrochloride salt; and compounds of formula VIII:



VIII.

The invention also provides methods for treating and preventing migraines (including classic migraines, common migraines, complicated migraines, cluster

headaches, menstrual migraines, premenstrual migraines, ophthalmic migraines, ophthalmoplegic migraines, fulgurating migraines, Harris' migraines, hemiplegic migraines, abdominal migraines) by administering at least one cholinesterase inhibitor, such as those described herein, and at least one migraine drug. The cholinesterase inhibitors and migraine drugs can be administered separately or in the form of a composition in the methods of treating and preventing migraines. Administering at least one cholinesterase inhibitor (e.g., donepezil, a stereoisomer thereof and/or a pharmaceutically acceptable salt thereof) and at least one migraine drug, either separately or in the form of a composition, provides an unexpectedly superior treatment for migraines.

When administered separately, the cholinesterase inhibitors and migraine drugs can be administered about the same time as part of an overall treatment regimen, i.e., as a combination therapy. "About the same time" includes administering the cholinesterase inhibitors and migraine drugs at the same time, at different times on the same day, or on different days, as long as they are administered as part of an overall treatment regimen. One skilled in the art would recognize that the unexpectedly superior results of the invention could be achieved by administering cholinesterase inhibitors and migraine drugs, for example, on alternating days.

Migraine drugs that can be used to prevent and/or treat migraines include, for example, estrogen, serotonin antagonists, non-steroidal antiinflammatory drugs (NSAIDs) (e.g., COX-1 inhibitors and/or COX-2 inhibitors), calcium channel blockers, beta-andrenergic blockers, anticonvulsants, and antidepressants (e.g., tricylcic antidepressants, monoamine oxidase inhibitors, and selective serotonin reuptake inhibitors). Estrogen is generally used for preventing and/or treating menstrual migraines and premenstrual migraines.

Exemplary migraine drugs that can be used to prevent and/or treat migraines include celecoxib, meloxicam, etodolac, rofecoxib, PNU-142633, vigabatrin, topiramate, montelukast (e.g., the sodium salt thereof), gabapentin, piroxicam (e.g., piroxicam betadex), valproate (e.g., the semisodium salt thereof), ketoprofen, diclofenac (e.g., the potassium salt), tiagabine, botulinum, nebivolol, lisinopril, nimodipine, tizanidine, zolmitriptan, sumatriptan (e.g., the succinate salt thereof), rizatriptan (e.g., the benzoate salt thereof), pizotifen, oxetorone, naratriptan, lomerizine

(e.g., the hydrochloride salt thereof), gepefrine, flunarizine, almotriptan, alpiropride, tolfenamic acid, migpriv, timolol (e.g., the maleate salt thereof), buclizine (e.g., the hydrochloride salt thereof), baclofen, methysergide (e.g., the maleate salt thereof), flunarizine (e.g., the hydrochloride salt thereof), cyproheptadine (e.g., the hydrochloride salt thereof), ergotamine (e.g., the tartrate salt thereof), lidocaine (e.g., the hydrochloride salt thereof), indoramin (e.g., the hydrochloride salt thereof), butorphanol, KT 2962, BMS 181885, ADDS-ergotamine, NPS-1776, GW-468816, triptan, Pharmaprojects No. 6313, MT-500, donitriptan (e.g., the mesylate salt thereof), ALX-0646, civamide, propanolol, zucapsaicin, CNS 5161, vofopitant, lanepitant, dapitant, ganaxolone, LY-53857, sergolexole (e.g., the maleate salt thereof), sumatriptan, MT-400, fluoxetine, (S)-fluoxetine, dihydroergotamine (e.g., the mesylate salt thereof), tonabersat, IS-159, BIBN-4096, metoclopramide, naproxen, MT-100 (e.g., a combination of metoclopramide and naproxen), dotarizine, frovatriptan, eletriptan, aspirin, ibuprofen, acetaminophen, amitryptiline, doxepin, ergot preparations, caffeine, cafergot (e.g., a combination of caffeine and ergotamine), codeine, meperidine, promethazine, atropine, phenobarbital, nifedipine, verapamil, chlorpromazine, lithium, prednisone, propranolol, phenelzine, mefenamic acid, flufenamic acid, LY334370, indomethacin, dichloralphenazone, isometheptene, butalbital, ketorolac, clonazepam, atenolol, metoprolol, nadolol, imipramine, nortripyline, diltiazem, valproic acid, divalproex, cyproheptadine, or pharmaceutically acceptable salts thereof.

The cholinesterase inhibitors and migraine drugs can be administered in the form of a pharmaceutically acceptable salt. Pharmaceutically acceptable salts are well known in the art and include those of inorganic acids, such as hydrochloride, sulfate, hydrobromide and phosphate; and those of organic acids, such as formate, acetate, trifluoroacetate, methanesulfonate, benzenesulfonate and toluenesulfonate. When certain substituents are selected, the compounds of the invention can form, for example, alkali metal salts, such as sodium or potassium salts; alkaline earth metal salts, such as calcium or magnesium salts; organic amine salts, such as a salt with trimethylamine, triethylamine, pyridine, picoline, dicyclohexylamine or N,N'-dibenzylethylenediamine. One skilled in the art will recognize that the compounds of the invention can be made in the form of any other pharmaceutically acceptable salt.

The invention provides compositions comprising at least one cholinesterase

inhibitor, such as those described herein, and at least one migraine drug, such as those described herein. The compositions preferably comprise one or more pharmaceutically acceptable carriers, as described herein. In preferred embodiments, the cholinesterase inhibitor is donepezil, a stereoisomer thereof and/or a pharmaceutically acceptable salt thereof.

The invention provides combinations comprising at least one cholinesterase inhibitor, such as those described herein, and at least one migraine drug, such as those described herein, wherein the at least one cholinesterase inhibitor and at least one migraine drug are separate pharmaceutical formulations that are administered as part of the same treatment regimen, i.e., combination therapy. In preferred embodiments, the cholinesterase inhibitor is donepezil, a stereoisomer thereof and/or a pharmaceutically acceptable salt thereof. The combination is preferably synergistic.

The invention provides pharmaceutical kits comprising one or more containers filled with one or more of the ingredients of the pharmaceutical compounds and/or compositions of the invention, including, one or more cholinesterase inhibitors (e.g., donepezil, stereoisomers thereof and/or pharmaceutically acceptable salts thereof) and one or more migraine drugs. The cholinesterase inhibitors and migraine drugs can be separate components in the kit or can be in the form of a composition in the kit. The kits can also include, for example, other compounds and/or compositions, a device(s) for administering the compounds and/or compositions, and written instructions in a form prescribed by a governmental agency regulating the manufacture, use or sale of pharmaceuticals.

The cholinesterase inhibitors can be prepared by processes that are known in the art and described, for example, in U.S. Patent No. 4,895,841, WO 98/39000, and Japanese Patent Application Nos. 4-187674 and 4-21670, the disclosures of each of which are incorporated by reference herein in their entirety. Donepezil hydrochloride, a preferred cholinesterase inhibitor for use in the methods described herein, is commercially available as ARICEPT® from Eisai Inc., Teaneck, NJ.

The migraine drugs are available from commercial sources, and methods of making the migraine drugs are known and described in the literature.

The dosage regimen for treating and preventing migraines with the cholinesterase inhibitors and, optionally, migraine drugs, can be selected in accordance

with a variety of factors, including the age, weight, sex, and medical condition of the patient, the severity of the migraines, the route of administration, pharmacological considerations such as the activity, efficacy, pharmacokinetic and toxicology profiles of the particular cholinesterase inhibitor and, optionally, migraine drug used, whether a drug delivery system is used and whether the cholinesterase inhibitor is administered as part of a drug combination (i.e., with one or more migraine drugs).

In preferred embodiments, the cholinesterase inhibitors are administered to treat or prevent migraines in doses of about 0.1 milligram to about 300 milligrams per day, preferably about 1 milligram to about 100 milligrams per day, more preferably about 5 milligrams to about 10 milligrams per day. The doses can be administered in one to four portions over the course of a day, preferably once a day. One skilled in the art will recognize that when the cholinesterase inhibitors are administered to children, the dose can be smaller than the dose administered to adults, and that the dose can be dependent upon the size and weight of the patient. In preferred embodiments, a child can be administered the cholinesterase inhibitors in doses of about 0.5 milligrams to about 10 milligrams per day, preferably about 1 milligram to about 3 milligrams per day.

In other preferred embodiments of the methods described herein, a physician can administer patients donepezil hydrochloride, which is commercially available as ARICEPT® (Eisai Inc., Teaneck, NJ), as tablets containing either 5 milligrams donepezil hydrochloride or 10 milligrams donepezil hydrochloride. The tablets can be administered one to about four times a day. In preferred embodiments, one 5 milligram or one 10 milligram ARICEPT® tablet is administered once a day for the methods described herein. One skilled in the art will appreciate that when donepezil hydrochloride is administered to children, the dose can be smaller than the dose that is administered to adults. In preferred embodiments, a child can be administered donepezil hydrochloride in doses of about 0.5 milligrams to about 10 milligrams per day, preferably about 1 milligram to about 3 milligrams per day.

The migraine drugs can be administered in therapeutically effective amounts that are known in the art, as described, for example, in standard medical texts, such as the *Physicians' Desk Reference* or the literature, the disclosures of which are incorporated by reference herein in their entirety.

The cholinesterase inhibitors and migraine drugs can be administered orally,

topically, parenterally, by inhalation (nasal or oral), or rectally in dosage unit formulations containing conventional nontoxic pharmaceutically acceptable carriers, adjuvants, and vehicles as desired. The term parenteral includes subcutaneous, intravenous, intramuscular, intrasternal injection, or infusion techniques. Preferably, the cholinesterase inhibitors are orally administered as tablets. When administered to children, the cholinesterase inhibitors are preferably orally administered in a liquid dosage form.

Injectable preparations, for example, sterile injectable aqueous or oleaginous suspensions, of the cholinesterase inhibitors and migraine drugs can be formulated according to the known art using suitable dispersing or wetting agents, suspending agents (e.g., methylcellulose, Polysorbate 80, hydroxyethylcellulose, acacia, powdered tragacanth, sodium carboxymethylcellulose, polyoxytehylene sorbitan monolaurate and the like), pH modifiers, buffers, solubilizing agents (e.g., polyoxyethylene hydrogenated castor oil, Polysorbate 80, nicotinamide, polyoxyethylene sorbitan monolaurate, Macrogol, an ethyl ester of castor oil fatty acid, and the like) and preservatives. The sterile injectable preparation can also be a sterile injectable solution or suspension in a nontoxic parenterally acceptable diluent or solvent, for example, as a solution in 1,3-butanediol. Among the acceptable vehicles and solvents that can be used are water, Ringer's solution, and isotonic sodium chloride solution. In addition, sterile, fixed oils are conventionally used as a solvent or suspending medium. For this purpose any bland fixed oil can be used including synthetic mono- or diglycerides, in addition, fatty acids, such as oleic acid, can be used in the preparation of injectables. The preparations can be lyophilized by methods known in the art.

Solid dosage forms for oral administration of the cholinesterase inhibitors and migraine drugs can include chewing gum, capsules, tablets, sublingual tablets, powders, granules and gels; preferably tablets. In such solid dosage forms, the active compound can be admixed with one or more inert diluents such as lactose or starch. As is normal practice, such dosage forms can also comprise other substances including lubricating agents such as magnesium stearate. In the case of capsules, tablets, and pills, the dosage forms can also comprise buffering agents. The tablets can be prepared with enteric or film coatings, preferably film coatings.

In addition to the active ingredient, the cholinesterase inhibitor tablets can

preferably comprise lactose monohydrate, corn starch, microcrystalline cellulose, hydroxypropyl cellulose, and magnesium stearate; while the film-coating on the tablet can preferably comprise talc, polyethylene glycol, hydroxpropyl methylcellulose, titanium dioxide, and, optionally, other coloring agents, such as yellow iron oxide.

Liquid dosage forms for oral administration of the cholinesterase inhibitors and migraine drugs can include pharmaceutically acceptable emulsions, solutions, suspensions, and syrups containing inert diluents commonly used in the art, such as water. Such compositions can also comprise adjuvants, such as wetting agents, emulsifying and suspending agents, and sweetening, flavoring, and perfuming agents.

For administration by inhalation, the cholinesterase inhibitors and migraine drugs can be delivered from an insufflator, a nebulizer or a pressured pack or other convenient mode of delivering an aerosol spray. Pressurized packs can include a suitable propellant. Alternatively, for administration by inhalation, the cholinesterase inhibitors and migraine drugs can be administered in the form of a dry powder composition or in the form of a liquid spray.

Suppositories for rectal administration of the cholinesterase inhibitors and migraine drugs can be prepared by mixing the active compounds with suitable nonirritating excipients such as cocoa butter and polyethylene glycols that are solid at room temperature and liquid at body temperature.

For topical administration to the epidermis, the cholinesterase inhibitors and/or migraine drugs can be formulated as ointments, creams or lotions, or as the active ingredient of a transdermal patch. The cholinesterase inhibitors and/or migraine drugs can also be administered via iontophoresis. Ointments, creams and lotions can be formulated with an aqueous or oily base with the addition of suitable thickening and/or gelling agents. Alternatively, ointments, creams and lotions can be formulated with an aqueous or oily base and can also contain one or more emulsifying agents, stabilizing agents, dispersing agents, suspending agents, thickening agents, and/or coloring agents. As creams or lotions, the cholinesterase inhibitors and/or migraine drugs can be mixed to form a smooth, homogeneous cream or lotion with, for example, one or more of a preservative (e.g., benzyl alcohol 1% or 2% (wt/wt)), emulsifying wax, glycerin, isopropyl palmitate, lactic acid, purified water, sorbitol solution. Such topically administrable compositions can contain polyethylene glycol 400. To form ointments,

the cholinesterase inhibitors and/or migraine drugs can be mixed with one or more of a preservative (e.g., benzyl alcohol 2% (wt/wt)), petrolatum, emulsifying wax, and Tenox (II) (e.g., butylated hydroxyanisole, propyl gallate, citric acid, propylene glycol). Woven pads or rolls of bandaging material, e.g., gauze, can be impregnated with the transdermally administrable compositions for topical application.

The cholinesterase inhibitors and/or migraine drugs can also be topically applied using a transdermal system, such as one of an acrylic-based polymer adhesive with a resinous crosslinking agent impregnated with the cholinesterase inhibitors and/or migraine drugs and laminated to an impermeable backing. For example, the cholinesterase inhibitors and/or migraine drugs can be administered in the form of a transdermal patch, such as a sustained-release transdermal patch. Transdermal patches can include any conventional form such as, for example, an adhesive matrix, a polymeric matrix, a reservoir patch, a matrix- or monolithic-type laminated structure, and are generally comprised of one or more backing layers, adhesives, penetration enhancers, and/or rate-controlling membranes. Transdermal patches generally have a release liner which is removed to expose the adhesive/active ingredient(s) prior to application. Transdermal patches are described in, for example, U.S. Patent Nos. 5,262,165, 5,948,433, 6,010,715 and 6,071,531, the disclosures of which are incorporated by reference herein in their entirety.

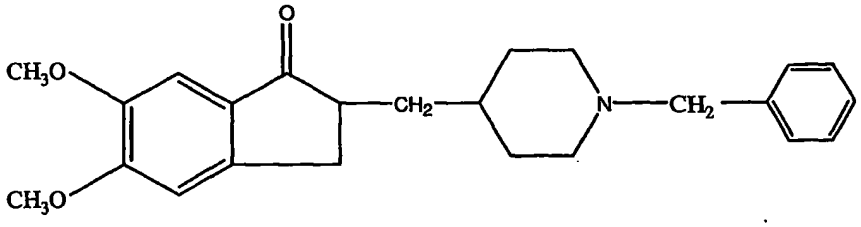
Each of the patents, patent applications, and publications cited herein are incorporated by reference herein in their entirety.

It will be apparent to one skilled in the art that various modifications can be made to the invention without departing from the spirit or scope of the appended claims.

Claims

What is claimed is:

1. A method for preventing or treating a migraine in a patient in need thereof comprising administering a therapeutically effective amount of a compound of formula (IV) or a pharmaceutically acceptable salt thereof:



(IV)

or a stereoisomer thereof.

2. The method of claim 1, wherein the migraine is a classic migraine.

3. The method of claim 1, wherein the migraine is a common migraine.

4. The method of claim 1, wherein the migraine is a complicated migraine.

5. The method of claim 1, wherein the migraine is a cluster headache.

6. The method of claim 1, wherein the migraine is a menstrual migraine.

7. The method of claim 1, wherein the migraine is a premenstrual migraine.

8. The method of claim 1, wherein the migraine is an ophthalmic migraine.

9. The method of claim 1, wherein the migraine is an ophthalmoplegic migraine.

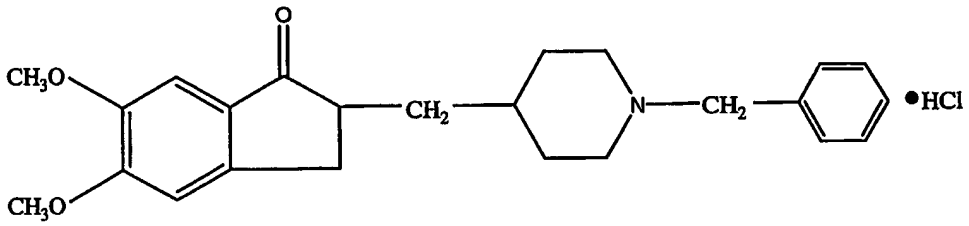
10. The method of claim 1, wherein the migraine is a fulgurating migraine.

11. The method of claim 1, wherein the migraine is a Harris' migraine.

12. The method of claim 1, wherein the migraine is a hemiplegic migraine.

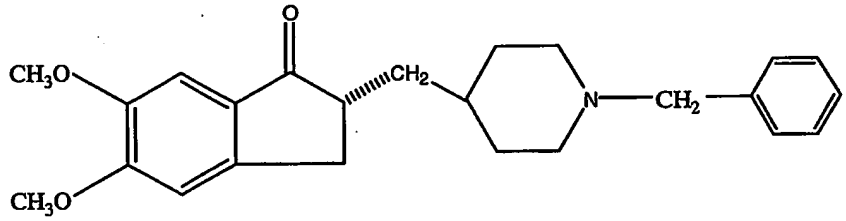
13. The method of claim 1, wherein the migraine is an abdominal migraine.

14. The method of claim 1, wherein the compound of formula (IV) is



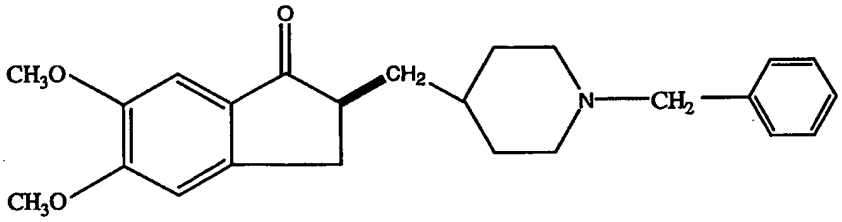
or a stereoisomer thereof.

15. The method of claim 1, wherein the compound of formula (IV) is a compound of formula (VI) or a pharmaceutically acceptable salt thereof:



(VI).

16. The method of claim 1, wherein the compound of formula (IV) is a compound of formula (VII) or a pharmaceutically acceptable salt thereof:



(VII).

17. The method of claim 1, wherein the compound of formula (IV) is administered in an amount of about 0.1 mg to about 100 mg.

18. The method of claim 17, wherein the compound of formula (IV) is administered in an amount of about 1 mg to about 100 mg.

19. The method of claim 18, wherein the compound of formula (IV) is

administered in an amount of about 5 mg to about 10 mg.

20. The method of claim 1, wherein the compound of formula (IV) is administered in an amount of about 5 milligrams.

21. The method of claim 1, wherein the compound of formula (IV) is administered in an amount of about 10 milligrams.

22. The method of claim 1, wherein the compound of formula (IV) is orally administered.

23. The method of claim 22, wherein the compound of formula (IV) is orally administered in the form of a tablet.

24. The method of claim 1, further comprising administering a pharmaceutically acceptable carrier.

25. The method of claim 1, further comprising administering at least one migraine drug.

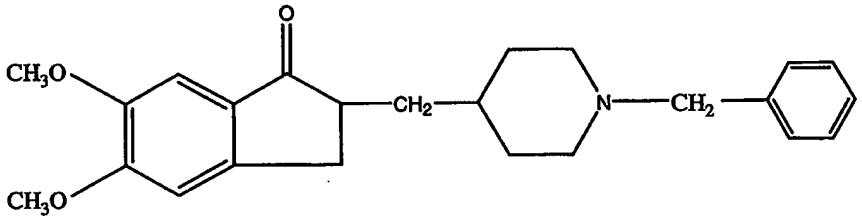
26. The method of claim 15, wherein the migraine drug is estrogen, a serotonin antagonist, a non-steroidal antiinflammatory drug, a calcium channel blocker, a beta-andrenergic blocker, an anticonvulsant, or an antidepressant.

27. The method of claim 26, wherein the non-steroidal antiinflammatory drug is a COX-2 inhibitor.

28. The method of claim 25, wherein the migraine drug is celecoxib, meloxicam, etodolac, rofecoxib, estrogen, PNU-142633, vigabatrin, topiramate, montelukast, gabapentin, ketoprofen, piroxicam, valproate, diclofenac, tiagabine, botulinum, nebivolol, lisinopril, nimodipine, tizanidine, zolmitriptan, sumatriptan, rizatriptan, pizotifen, oxetorone, naratriptan, lomerizine, gepefrine, flunarizine, almotriptan, alpiropride, tolfenamic acid, migpriv, timolol, buclizine, baclofen, methysergide, flunarizine, cyproheptadine, ergotamine, lidocaine, indoramin, butorphanol, KT 2962, BMS 181885, ADDS-ergotamine, NPS-1776, GW-468816, triptan, Pharmaprojects No. 6313, MT-500, donitriptan, ALX-0646, civamide, propanolol, zucapsaicin, CNS 5161, vofopitant, lanepitant, dapitant, ganaxolone, LY-53857, sergolexole, sumatriptan, MT-400, fluoxetine, (S)-fluoxetine,

dihydroergotamine, tonabersat, IS-159, BIBN-4096, metoclopramide, naproxen, MT-100, dotarizine, frovatriptan, eletriptan, aspirin, ibuprofen, acetaminophen, amitryptiline, doxepin, ergot preparations, caffeine, cafergot, codeine, meperidine, promethazine, atropine, phenobarbital, nifedipine, verapamil, chlorpromazine, lithium, prednisone, propranolol, phenelzine, mefenamic acid, flufenamic acid, LY334370, indomethacin, dichloralphenazone, isometheptene, butalbital, ketorolac, clonazepam, atenolol, metoprolol, nadolol, imipramine, nortripyline, diltiazem, valproic acid, divalproex, cyproheptadine, or a pharmaceutically acceptable salt thereof.

29. A composition comprising a therapeutically effective amount of a compound of formula (IV) or a pharmaceutically acceptable salt thereof:

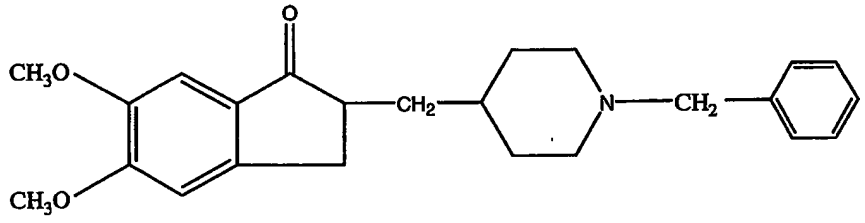


(IV)

or a stereoisomer thereof; and

a therapeutically effective amount of at least one migraine drug.

30. A combination comprising a therapeutically effective amount of a compound of formula (IV) or a pharmaceutically acceptable salt thereof:

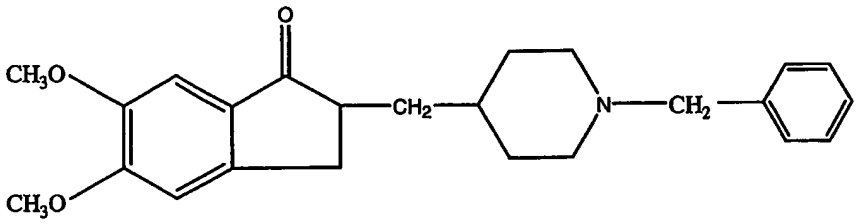


(IV)

or a stereoisomer thereof; and

a therapeutically effective amount of at least one migraine drug.

31. A kit comprising a therapeutically effective amount of a compound of formula (IV) or a pharmaceutically acceptable salt thereof:



(IV)

or a stereoisomer thereof; and

a therapeutically effective amount of at least one migraine drug.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US02/29734

A. CLASSIFICATION OF SUBJECT MATTER

IPC(7) : A61K 31/55, 31/445
US CL : 514/212.01, 319, 321

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
U.S. : 514/212.01, 319, 321

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
Please See Continuation Sheet

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 6,103,218 A (BRUCKER et al.) 15 August 2000, (15.08.2000) see entire document.	1-31
Y	WO 99/23077 A1 (PFIZER PRODUCTS INC.) 14 May 1999 (14.05.1999) see abstract, page 6, see claims.	1-31

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
02 December 2002 (02.12.2002)	31 JAN 2003
Name and mailing address of the ISA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231 Facsimile No. (703)305-3230	Authorized officer Donna Jagoe Telephone No. (703) 308-1235

Form PCT/ISA/210 (second sheet) (July 1998)

INTERNATIONAL SEARCH REPORT

PCT/US02/29734

Continuation of B. FIELDS SEARCHED Item 3:

STN file registry and file cluster MEDICINE, Search Terms: cholinesterase inhibitor, indol?, migraine, headache, pain, antispasmodic, ambenonium or atropine or edrophonium or demecarium or donepezil or isoflurophate or neostigmine or physostigmine or pyridostigmine or tacrine.